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HCV/HIV Co-infection and Responses to Initial Antiretroviral Treatment

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Abstract

Objective—To explore the relationship between HCV/HIV co-infection and responses to initial antiretroviral treatment (ART)

Methods—Four AIDS Clinical Trials Group HIV treatment studies' data were combined to compare initial ART responses between HCV/HIV co-infected and HIV mono-infected patients as evaluated by virologic failure, CD4 measures, occurrence of AIDS/death and Grade 3/4 safety events, using Kaplan-Meier estimates and proportional hazard, regression and mixed effects models, adjusting for baseline covariates.

Results—Of the 3041 included subjects, 81% were male, 19% had prior history of AIDS, the median (25th, 75th percentile) baseline HIV RNA was 4.72 (4.38, 5.18) log₁₀ copies/mL and the median (25th, 75th percentile) baseline CD4 was 216.0 (76.5, 327.0) cells/μL. The 279 HCV/HIV co-infected were older (44 vs. 37 years), more likely to be black non-Hispanic (47% vs. 36%) and history/current intravenous drug user (52% vs. 5%) than the 2762 HIV mono-infected subjects (All P-values < 0.001). HCV/HIV co-infection was associated with earlier virologic failure, hazard ratio (HR) (95% confidence interval): 1.43 (1.07, 1.91); smaller mean CD4 increase and CD4% increase (-33.8 (-52.2, -15.4) cells/μL and -1.16% (-1.43%, -0.89%), respectively) over a median of 132 weeks follow-up; earlier occurrence of Grade 3/4 safety event, HR 1.51 (1.26, 1.81); and increased AIDS/mortality, HR 2.10 (1.31, 3.37). Treatment effects comparing antiretroviral regimens were not significantly different by HCV/HIV co-infection status.

Conclusions—HCV/HIV co-infection is associated with attenuated response to ART. Results support earlier initiation of HIV therapy and increased monitoring of those initiating ART with HCV/HIV co-infection.

Keywords

HCV/HIV Co-infection; ART; Treatment Naïve; Early Virologic Failure; CD4 Responses

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Introduction

Approximately 30% of HIV-1-infected subjects in the United States are co-infected with hepatitis C virus (HCV) [1, 2]. HCV/HIV is also causing health burden worldwide [3, 4]. Despite extensive research and subsequently better understanding of the negative effects of HIV infection on HCV replication, persistence and liver fibrogenesis [5-8], whether HCV is associated with HIV progression continues to be debated. Natural history studies show that, prior to antiretroviral treatment (ART) initiation, HCV/HIV co-infected subjects have similar HIV disease progression compared to HIV mono-infected subjects [2, 9, 10]. However, inconsistent results have been reported for CD4 and HIV virologic responses to ART as well as HIV progression and mortality. While some studies have shown that HCV co-infection is associated with either smaller CD4 increases after initiation of ART [11-16] or a delayed CD4 response [17], other studies report early detected differences in CD4 response wane over time [4, 18]. Many studies have not found such an association [3, 19-25]. Most of the aforementioned studies did not report on or find any association between HCV/HIV co-infection and subjects' HIV-1 virologic responses [12, 13, 26]. In a recent meta-analysis, HCV/HIV co-infection was not found to be related to AIDS-defining endpoints [15], consistent with some previous studies [27, 28] although other studies have shown the opposite [29]. These inconsistent results may be explained by relatively small sample sizes of some cohort studies, the heterogeneous populations studied, the limited baseline information collected and the different ART regimens studied, including many regimens that are no longer in use.

This manuscript reports on analyses combining data from four randomized studies of initial antiretroviral regimens in HIV-1-infected treatment-naïve in the United States by the AIDS Clinical Trial Group (ACTG). The aims of this cross-study analysis were to evaluate the association of HCV/HIV co-infection with subjects' responses to ART initiation from different perspectives, including virologic responses, immunologic responses, safety concerns and clinical outcomes, and to assess whether HCV/HIV co-infection modifies ART treatment effect when comparing specific regimens.

Methods

Study Design

Randomized treatment arms, sample sizes and extent of follow-up of the four included studies, ACTG A5073 [30, 31], A5095 [32], A5142 [33] and A5202 [34-36], are detailed in cited published papers and summarized in Table 1. These studies were approved by site Institutional Review Boards; participants provided written informed consent.

In the analyses, data from two treatment arms were excluded due to their limited applicability: in A5073, one arm received directly observed therapy; in A5095, the triple nucleoside reverse transcriptase inhibitor arm was terminated early due to its inferiority to efavirenz (EFV)-containing arms [32]. Subjects were followed by study specified schedules, typically at 12-week intervals, which were independent of whether the subjects were on their initially assigned regimen. Analyses were restricted to subjects with at least one follow-up HIV-1 RNA measurement. Race/ethnicity is a potential confounder for the association

between HCV/HIV co-infection and subjects' responses to ART. Due to small sample sizes, subjects with race/ethnicity other than white non-Hispanic, black non-Hispanic or Hispanic were excluded from analyses.

Liver Related Measurements

All four studies required HCV serology as well as HBV test results within one year prior to study entry, except for subjects enrolled into A5095 under protocol version 1.0. Since HCV RNA was not uniformly available, those with positive HCV antibody results between 1 year prior to and 4 weeks post study entry were assumed to have chronic HCV infection prior to ART initiation. Subjects with a first HCV serology result after 4 weeks post study entry, mainly from A5095, were excluded from the primary analyses but included in sensitivity analyses. Subjects with positive HBV surface antigen were defined as having chronic HBV before initiation of ART. All four studies collected baseline aspartate aminotransferase (AST) and alanine transaminase (ALT) at entry. Entry criteria for the studies' required that AST and ALT be ≤ 5 times the upper limit of normal (ULN) and total bilirubin ≤ 2.5 ULN (except A5095). In absence of liver biopsy or transient elastometry (TE) results, baseline AST/Platelet Ratio Index (APRI) [37] and FIB-4 [38] were calculated to reflect the severity of the liver disease before ART initiation across studies, acknowledging that these surrogate biomarkers may not be as accurate as biopsy or TE results. All four studies specified any condition, including active drug/alcohol use, which at the discretion of the local investigator might compromise subjects' ability to participate in the study as study entry exclusion criteria.

Outcomes

Time-related endpoints were calculated from randomization. Virologic response for this analysis was measured by time to virologic failure, defined as two consecutive plasma HIV-1 RNA either ≥ 1000 copies/mL at or after week 16 and before week 24, or ≥ 200 copies/mL at or after week 24. Subjects who discontinued the study at week 4 with HIV-1 RNA > 50 copies/mL and $< 0.5 \log_{10}$ copies/mL lower than baseline and those discontinued at week 8 with HIV-1 RNA > 50 copies/mL and $< 1 \log_{10}$ copies/mL lower than baseline were considered having virologic failures at weeks 4 and 8, respectively. Immunologic responses were analyzed as the average CD4 count, CD4% and their changes from baseline. Clinical outcomes were times to first of new on-study AIDS-defining event or death regardless of cause, and to death alone. The safety-related endpoint was time to first Grade 3/4 signs/symptoms or laboratory abnormality (toxicity rating scale developed by the Division of AIDS [version 1.0, December 2004]) that was at least one grade higher than at baseline. Adherence to the prior 7 days of ART was collected via self-report at 24-week intervals throughout the four studies. The adherence scores at each measurement time point for subjects still in follow-up were grouped into four levels: 1) 100% adherent; 2) $< 100\%$ adherent; 3) Not on medication; and 4) Unknown.

Statistical Analysis

Baseline demographics and clinical characteristics were compared between HCV/HIV co-infected and HIV mono-infected subjects using Wilcoxon rank sum test for continuous variables rather than normal distribution assumption based parametric analysis to account

for skewed data and χ^2 test for categorical variables. Baseline covariates, including age, sex, race/ethnicity, HIV-1 RNA (grouped *a priori* into < 10,000, 10,000 -< 100,000, 100,000 -< 200,000 and 200,000 copies/mL), CD4 counts (< 50, 50 -< 200, 200 -< 350, 350 -< 500 and 500 cells/ μ L), prior AIDS history, active or history intravenous drug user (IVDU) and chronic HBV infection, were controlled for in regression analyses regardless of their significance between groups at baseline. Time-to-event outcomes were compared based on log-rank tests stratified by treatment arms; event time percentiles were estimated by the Kaplan-Meier method. Cox proportional hazard models, stratified by treatment arms, were fit with and without adjusting for baseline covariates. Antiretroviral regimens were grouped according to their dual nucleoside reverse transcriptase inhibitors (NRTIs) and the third drug in the regimen, i.e., protease inhibitors (PIs, all ritonavir boosted) versus the non-NRTI efavirenz (EFV) use. Whether HCV/HIV co-infection modifies the antiretroviral treatment effect when comparing specific regimens, hereafter referred to as the “treatment modification effect”, was evaluated in Cox proportional hazard models stratified by study by testing for an interaction between antiretroviral regimen groups and HCV status. CD4 measurements in every 24-week interval were compared between groups using linear regressions controlling for baseline covariates. Repeated CD4 measurements during follow-up were modeled using linear mixed effects models with a random subject effect. In post-hoc regression analyses, interactions of HCV/HIV co-infection status with baseline HIV-1 RNA on virologic response and with baseline CD4 counts on CD4 responses were evaluated adjusting for other baseline covariates. Adherence (100% vs. <100%) of those who were still on ART was compared between HCV/HIV co-infected and HIV mono-infected subjects using logistic regressions at weeks 24, 48, 72 and 96. Repeated measurements of adherence during follow-up were modeled using generalized estimating equations with a compound symmetry covariance structure. Additional analyses on subjects' responses to ART controlled for the most recent adherence (with 4 categories) in addition to baseline covariates mentioned above. All comparisons were conducted with a two-sided significance level of 0.05, without adjusting for multiplicity.

Results

Baseline Characteristics

Of 3041 white, black or Hispanic subjects with available baseline HCV serology, the majority were from A5202 and A5142 (57% and 23%, respectively), 279 (9.2%) were HCV seropositive and assumed to be co-infected (Table 2). Compared to HIV mono-infected, HCV/HIV co-infected subjects were significantly older (median age 44 vs. 37 years), more likely to be black non-Hispanic (47% vs. 36%) and prior/current IVDU (52% vs. 5%; All P-values < 0.001). HCV/HIV co-infection was also associated with significantly higher AST, ALT, FIB-4 and APRI (All P-values < 0.001). The median (25th, 75th percentile) FIB-4 and APRI scores among co-infected subjects were 1.41 (0.92, 2.41) and 0.45 (0.28, 0.90) respectively, indicating mild to moderate liver fibrosis [37, 38]. Thirteen percent of HCV/HIV co-infected subjects based on FIB-4, or 10% based on APRI, had high values of non-invasive markers, suggesting severe liver fibrosis.

Virologic Response

HCV/HIV co-infected subjects had significantly earlier time to virologic failure after initiating their ART than HIV mono-infected subjects (log-rank P-value < 0.001, Figure 1A), with the estimated time (95% confidence interval [CI]) to when 20% of subjects have experienced a HIV virologic failure of 48 (32, 72) weeks in HCV/HIV co-infected compared to 112 (96, 136) weeks in HIV mono-infected subjects. The hazard ratios (HR, 95% CI) of having virologic failure for HCV/HIV co-infected versus HIV mono-infected subjects were 1.60 (1.27, 2.02) and 1.43 (1.07, 1.91) before and after adjusting for baseline covariates, respectively. The association of HCV/HIV co-infection with virologic failure was marginally significantly different by baseline HIV-1 RNA level (Interaction P-value = 0.078), primarily among the 329 subjects (27 co-infected vs. 302 mono-infected) with baseline HIV-1 RNA <10,000 copies/mL with a HR (95% CI) of 3.06 (1.56, 5.99). These subjects were more likely to be black non-Hispanic, current/history IVDU and HBV-infected (Supplementary Table 1). Within groups with higher baseline HIV-1 RNA (≥10,000 copies/mL), the HR of time to virologic failure between HCV/HIV co-infected and HIV mono-infected subjects did not individually reach statistical significance, albeit co-infected subjects had consistently higher hazards (all HR point estimates > 1.0, Figure 1B). There was no significant treatment modification effect by HCV/HIV co-infection status (P-value = 0.75 for NRTI groups and 0.66 for the third drug in regimen groups, Supplementary Table 2).

CD4 Response

At baseline, HCV/HIV co-infected subjects had on average slightly lower CD4 counts and lower CD4%, possibly due to advanced liver disease and hypersplenism, but the differences were not statistically significant (P-value = 0.14 and 0.44, respectively, Table 3). After ART initiation, HCV/HIV co-infected subjects had lower mean CD4 count and smaller CD4 increase from baseline, as well as lower mean CD4% and smaller CD4% increase from baseline than HIV mono-infected subjects at all follow-up weeks (Figure 2). At week 48, based on the 2,666 subjects with CD4 data and data on baseline covariates, HCV/HIV co-infected subjects had a lower mean CD4 count of 32.8 (95% CI 9.7, 56.9) cells/μL and a smaller increase from baseline of 27.8 (5.9, 49.8) cells/μL compared to HIV mono-infected subjects, P-value = 0.005 and 0.013 respectively. Similarly, the HCV/HIV co-infected subjects had a lower mean CD4% of 1.28 (0.16, 2.40), P-value = 0.025 and a smaller mean increase in CD4% from baseline of 0.96 (0.08, 1.84), P-value = 0.032. The differences were maintained through week 144 after controlling for baseline CD4 counts and other baseline covariates in the regression analyses (Table 3). In follow-up after week 144, the differences between HCV/HIV co-infected and HIV mono-infected subjects did not reach statistical significance (results not included), but sample sizes were small, especially for the HCV/HIV co-infected group. Among 3,037 subjects with baseline CD4 and at least one CD4 measurement after baseline, the median (25th, 75th percentile) follow-up time was 132 (88, 168) weeks. Based on longitudinal modeling of all CD4 measurements during follow-up, HCV/HIV co-infected subjects had, over time, a mean of 39.2 (19.9, 58.4) cells/μL lower CD4 count and 33.8 (15.4, 52.2) cells/μL smaller CD4 increase from baseline, and a mean of 1.13 (0.82, 1.44) lower CD4% and 1.16 (0.89, 1.43) smaller CD4% increase from baseline than HIV mono-infected subjects (All P-values < 0.001). Excluding CD4 measurements

after subjects experienced virologic failure, these differences decreased slightly and some cross sectional associations were not as significant, in particular for change in CD4% (Table 3). However, in longitudinal modeling HCV/HIV co-infection remained significantly associated with lower mean CD4 count and smaller CD4 count increase from baseline, as well as lower CD4% and smaller CD4% increase from baseline (All P-values < 0.001, Table 3). The association of HCV/HIV co-infection with the blunted CD4 response was not significantly different by baseline CD4 levels (categorized, P-values > 0.34 at different weeks and longitudinally). There was no evidence that HCV/HIV co-infection modified the treatment effect on CD4 responses when comparing specific ART regimens (P-value = 0.20 for NRTI groups and 0.88 for the third drug in regimen groups).

AIDS-Defining Event or Death

Eleven percent of HCV/HIV co-infected subjects developed an AIDS-defining event or died while in study follow-up, compared to 5% in HIV mono-infected subjects (P-value < 0.001, Supplementary Table 3), with a HR (95% CI) of 2.11 (1.42, 3.13) and 2.10 (1.31, 3.37) before and after controlling for baseline covariates (Supplementary Figure 1A). The increased hazard was primarily driven by mortality (Supplementary Figure 1B), with a HR (95% CI) of mortality at 5.45 (3.01, 9.85) and 5.14 (2.48, 10.67) before and after adjusting for baseline covariates. HCV/HIV co-infected subjects had more accidents, suicides or substance abuse related deaths compared to HIV mono-infected subjects (41.2% vs. 20.6%, Supplementary Table 4).

Occurrence of Grade 3/4 Safety Events

Of the 279 HCV/HIV co-infected subjects, 65% experienced at least one Grade 3/4 safety event compared to 53% in HIV mono-infected group (P-value < 0.001), largely due to elevated AST or ALT (14% vs. 3%, P-value < 0.001, Supplementary Table 5). The median time to experiencing a Grade 3/4 safety event was 33 (24, 50) weeks in HCV/HIV co-infected compared to 97 (86, 112) weeks in HIV mono-infected subjects (Supplementary Figure 2). The HR (95% CIs) were 1.57 (1.34, 1.84) and 1.51 (1.26, 1.81) before and after adjusting for baseline covariates, respectively. Excluding AST and ALT, the occurrence of other Grade 3/4 safety events was not significantly different between HCV/HIV co-infected vs. HIV mono-infected subjects (P-value = 0.37). However, HCV/HIV co-infected subjects experienced non-ALT/AST Grade 3/4 safety events earlier than HCV un-infected subjects (PH model P-value=0.016 and 0.068 before and after adjusting for baseline covariates, Supplementary Table 5 and Figure 2). There was no significant HCV treatment modification effect for the occurrence of Grade 3/4 safety events, both excluding AST/ALT: P-value = 0.14 for NRTI groups and 0.48 for the third drug in regimen groups; and considering AST/ALT alone: P-value = 0.80 for NRTI groups and 0.83 for the third drug in regimen groups (Supplementary Table 6). The earlier time to Grade 3/4 safety event in the atazanavir/ritonavir-containing regimens as compared to EFV containing regimens was primarily due to expected elevated total bilirubin (Supplementary Table 6). Excluding total bilirubin, this difference was no longer statistically significant.

Adherence

Supplementary Table 7 summarizes self-reported adherence (100% adherent vs. <100% adherent) among those who were still on ART at weeks 24, 48, 72 and 96, by HCV/HIV co-infection status. At week 24 among those on ART, 91% of HCV/HIV co-infected subjects had 100% adherence compared to 87% among HIV mono-infected subjects. Controlling for baseline covariates, HCV/HIV co-infection was associated with increased odds of self-reported perfect adherence with an odds ratio (95% CI) of 1.73 (1.02, 2.93), P-value = 0.012. At subsequent follow-up weeks, HCV/HIV co-infected subjects were less likely to adhere perfectly, although such adherence remained high. Adjusting for baseline covariates, the difference in adherence between HCV/HIV co-infected and HIV mono-infected subjects was not significant at weeks 48 ($p = 0.73$), 72 ($p = 0.35$), 96 ($p = 0.48$) or longitudinally ($p = 0.09$). The observed significant differences between HCV/HIV co-infected and HIV mono-infected subjects in time to HIV-1 virologic failure, subjects' CD4 response, time to AIDS defining endpoint or death, time to death only and time to Grade 3/4 safety events were retained after controlling for the most recent adherence score in addition to baseline covariates (All P-values = 0.009).

Discussion

The reported analyses combined data from four ACTG randomized antiretroviral treatment trials with relatively homogeneous populations. The randomization, rigorous study monitoring and extensive and similar data collection from these clinical trials (Supplementary Table 8) provided a unique opportunity to systematically examine the association of HCV/HIV co-infection with response to ART. HCV/HIV co-infection before ART initiation was significantly associated with earlier time to virologic failure and attenuated CD4 responses including both blunted CD4 count recovery and smaller CD4% increase through 144 weeks. The association of HCV/HIV co-infection with attenuated CD4 responses was retained when restricting analysis to data from subjects while not failing virologically. This may be clinically relevant as HCV/HIV co-infection was also significantly associated with accelerated HIV disease progression with a higher risk of developing a new AIDS-related diagnosis or death.

Our results from data on randomized trials were consistent with results from the large observational Swiss HIV cohort study [11] as well as with other smaller cohort studies [12, 13]. The observed persistently attenuated CD4 T cell responses could be related to worse adherence and higher rates of virologic failure, but this is unlikely since the association remained strong even when limiting analysis to those not failing virologically. Alternative mechanisms may be related to the chronic immune activation reflected by elevated CD38/HLA-DR T cells in HCV/HIV co-infected subjects [39-41]. Regardless of the mechanism, these findings have important implications in the clinic. Both the International Antiviral Society-USA Panel [42] and the Department of Health and Human Services' HIV treatment guidelines [43] suggest that HCV infection might influence the decision as to when ART should be started, which is primarily justified by the fact that it might influence HCV disease progression. The results from this study further demonstrate that HCV/HIV co-infection is associated with increased risk of clinical progression and an attenuated CD4

response to ART, both of which would also argue for earlier initiation of therapy in this patient population based upon parameters relevant to HIV disease progression.

The better adherence at week 24 among HCV/HIV co-infected subjects may reflect a selection bias, i.e., HCV/HIV co-infected subjects, considered having a high risk of poorer adherence due to substance abuse, for example, may have been scrutinized more closely prior to enrollment. Consequently, HCV/HIV co-infected subjects enrolled into the randomized trials may have been more likely to adhere to their ART than those who were not enrolled. The exclusion criteria of select conditions, including active drug/alcohol usage that might affect subjects' adherence, may also contribute to such a selection bias.

The analyses took advantage of the randomization of the ART regimens and assessed the possible treatment modification effects of ART by HCV/HIV co-infection status. As there was no significant evidence that HCV/HIV co-infection was a treatment effect modifier when comparing antiretroviral regimens, our results do not indicate that HCV/HIV co-infection would need to be considered when choosing among the regimens included in the studies analyzed. However, the relatively small sample size in the HCV/HIV co-infected group resulted in wide CIs for outcome measures, in particular in subgroup analyses. Consequently, important modification effects could be missed.

Our analyses have several limitations. First, HCV/HIV co-infection status was determined by the serology result alone without confirmation by detection of HCV RNA and due to the lack of liver biopsy or TE results, severity of liver disease was limited to APRI and FIB-4 measurements. Subjects with positive HCV serology results may have included both subjects with cleared HCV and chronic HCV infections; although literature indicates that over 90% of HCV infections progress to chronic infection in HIV-infected subjects [19]. Nevertheless, because of this our results may be conservative as true associations between HCV co-infection and reduced ART responses might have been diluted by the inclusion of those that had cleared HCV infection self-clearers in the HCV co-infected group [2]. The opposite may also happen, where HCV/HIV co-infected subjects with low CD4 counts could have false negative serology result. Misclassification of these subjects as HIV mono-infected would also dilute the detected difference between HCV/HIV co-infected and HIV mono-infected subjects. The impact of using surrogates markers for severity of liver disease on the outcome of this study is less clear but certainly would not substantially alter the primary findings of the study. Second, in our primary analyses, only data from subjects with HCV infection status assessed between one year prior to and within 4 weeks after randomization at study entry were included. Sensitivity analyses of time to virologic failure and CD4 responses including data from additional 411 subjects with HCV serology results obtained after 4 weeks post study entry, mainly from A5095 where serology was not carried out under protocol version 1.0, showed consistent results (data not shown). Third, explicit laboratory based inclusion criteria in all four trials could have resulted in exclusion of subjects with significant transaminase elevation or hyperbilirubinemia, to whom the current result may not be applicable. The trial inclusion criteria may also explain the smaller proportion of HCV/HIV co-infection (9.2%) than the prevalence previously reported [1]. Lastly, among the 3,041 subjects, 17 subjects were reported to have received pegylated interferon and ribavirin on study, although use of these drugs was not specifically targeted to

be collected by the protocols. Excluding these subjects from the analysis did not change the results (data not shown). With the rapidly evolving field of direct antiviral agents for treatment of chronic HCV infection, the association of HCV/HIV co-infection with HIV disease progression also needs to be evaluated in the context of HCV treatment.

This study provides unique data from well characterized patients on the relationship between HCV/HIV co-infection and response to ART. The earlier time to virologic failure results argue for close monitoring of ART treatment effect and HIV disease progression in this population and the blunted immunologic responses support an earlier initiation of ART in HCV/HIV co-infected subjects to optimize their on-treatment CD4 counts. Further research is needed to determine whether early treatment of HCV in HCV/HIV co-infected subjects would be associated with improved responses to ART and clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Time to Virologic Failure (A) Probability of virologic failure by HCV Status (Solid line: HCV/HIV; Dotted line: HIV); (B) Estimated Hazard Ratio for VF between HCV/HIV co-infected and HIV mono-infected subjects by Baseline HIV-1 RNA Viral Load Adjusted for Baseline Covariates

Figure 2. Estimated Mean (95% CI) of (A) CD4 counts; (B) CD4 increase from baseline; (C) CD4%; (D) CD4% increase from baseline after initiation of ART at different scheduled weeks by HCV status (Solid line: HCV/HIV; Dotted line: HIV)

Summary of the ART-naïve Studies Included

Table 1

Parent Study	ART Regimens		Sample Size (% of Total)				Follow-up (person-year)	
	NRTI	PI or NNRTI	By arm	Total	HCV/HIV	HIV		Missing
A5073	FTC + d4T XR or TDF ¹	LPV/r BID	159					
	FTC + d4T XR or TDF ¹	LPV/r QD	161	402	52 (12.9%)	344 (85.6%)	6 (1.5%)	260
	FTC + d4T XR or TDF ^{1,2}	LPV/r QD	82					
A5095 ³	ABC/3TC/ZDV	EFV	383					
	ABC/3TC/ZDV ⁴		382	1147	55 (4.8%)	415 (36.2)	677 (59.0%)	694
	3TC /ZDV	EFV	382					
A5142		LPV/r BID + EFV	250					
	3TC + ZDV or d4T XR or TDF ¹	LPV/r BID	253	753	84 (11.2%)	649 (86.2%)	20 (2.7%)	1471
	3TC + ZDV or d4T XR or TDF ¹	EFV	250					
A5202	FTC/TDF	EFV	464					
	FTC/TDF	ATV/r	465	1857	134 (7.2%)	1705 (91.8%)	18 (1.0%)	4566
	ABC/3TC	EFV	465					
	ABC/3TC	ATV/r	463					

ART: antiretroviral therapy; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor; FTC:emtricitabine; ABC:abacavir; 3TC:lamivudine; ZDV: zidovudine; d4T XR: stavudine extended release; TDF:tenofovir disoproxil fumarate; LPV/r:lopinavir/ritonavir; ATV/r:atazanavir/ritonavir; EFV:efavirenz; BID: Twice a day; QD: Once a day;

- ¹ Non-randomized NRTI regimens; All studies were stratified by RNA: <100,000 vs. 100,000 copies/mL;
- ² Direct observing treatment arm, excluded from the analysis;
- ³ A5095 protocol version 1.0 did not require HCV Antibody testing at study entry (was collected later);
- ⁴ Terminated early by the study DSMB due to its inferiority for virologic outcome, excluded from the analysis;

Table 2

Baseline characteristics of subjects by HCV co-infection status

Characteristic	HIV (N=2762)	HCV/HIV (N=279)	Total (N=3041)	P-Value
ACTG Study				
A5073	258 (9%)	38 (14%)	296 (10%)	**
A5095	256 (9%)	40 (14%)	296 (10%)	
A5142	623 (23%)	81 (29%)	704 (23%)	
A5202	1,625 (59%)	120 (43%)	1,745 (57%)	
Age (years)	Median (Q1, Q3)	44 (39, 49)	38 (31, 45)	<.001*
Race/Ethnicity[†]	White Non-Hispanic	90 (32%)	1,197 (39%)	**
	Black Non-Hispanic	132 (47%)	1,117 (37%)	<.001
	Hispanic	57 (20%)	727 (24%)	
Sex	Male	227 (81%)	2,472 (81%)	0.974
Prior history of AIDS	Yes	523 (19%)	571 (19%)	0.480
Previous/Current IV drug use	Yes	142 (5%)	286 (9%)	**
Baseline log₁₀ RNA(copies/mL)	Median (Q1, Q3)	4.74 (4.38, 5.10)	4.72 (4.38, 5.18)	0.688*
Baseline RNA (copies/mL)	<10,000	302 (11%)	329 (11%)	
	10,000-<100,000	1,601 (58%)	1,768 (58%)	
	100,000-<200,000	268 (10%)	308 (10%)	
	200,000	591 (21%)	636 (21%)	
Baseline CD4 (cells/μL)	Median (Q1, Q3)	204.5 (76.5, 296.0)	216.0 (76.5, 327.0)	0.076*
	<50	556 (20%)	609 (20%)	
	50-<200	714 (26%)	794 (26%)	
	200-<350	896 (32%)	1,003 (33%)	
	350-<500	421 (15%)	449 (15%)	
	500	171 (6%)	182 (6%)	
AST (U/L)	N	2,639	2,893	
	Median (Q1, Q3)	29 (23, 39)	30 (23, 41)	<.001*
ALT (U/L)	N	2,641	2,895	
	Median (Q1, Q3)	31 (21, 46)	31 (21, 48)	<.001*
FIB-4	N	2,611	2,860	
		249		<.001*

Characteristic	HIV (N=2762)	HCV/HIV (N=279)	Total (N=3041)	P-Value
APRI	Median (Q1, Q3)	1.41 (0.92, 2.41)	0.92 (0.61, 1.37)	<.001*
	No/Mild fibrosis(< 1.45)	130 (52%)	2,217 (78%)	
	Indeterminate (1.45 - 3.25)	86 (35%)	550 (19%)	
	Fibrosis (> 3.25)	33 (13%)	93 (3%)	
	N	249	2,862	
	Median (Q1, Q3)	0.45 (0.28, 0.90)	0.32 (0.21, 0.51)	
	No/Mild fibrosis(< 0.42)	117 (47%)	1,888 (66%)	
HBsAg	Indeterminate (0.42 - 1.5)	106 (43%)	887 (31%)	0.235**
	Fibrosis (> 1.5)	26 (10%)	87 (3%)	
	N	268	3016	
	Positive	12 (4%)	98 (3%)	

* Wilcoxon Test;

** Chi-Square Test;

† Analysis were restricted to White, Black and non-Hispanic;

$$FIB-4 = \frac{Age(yr) \times AST(U/L)}{Platelet(10^9/L) \times ALT^{1/2}(U/L)}; APRI = \frac{AST}{ULN} \times \frac{100}{Platelet(mm^3)}; HBsAg: HBV Surface Antigen$$

AST: aspartate aminotransferase; ALT: alanine transaminase;

Table 3
Regression Results of Mean Differences in CD4 Count, CD4 Change, CD4% and CD4% Change between HCV Co-infected vs. Un-infected Subjects, Adjusting for Baseline Covariates

HCV/HIV vs. HIV		CD4 (cells/ μ L)		CD4 Change (cells/ μ L)		CD4%		CD4% Change	
Week		Mean Difference (95% CI)	P-value	Mean Difference (95% CI)	P-value	Mean Difference (95% CI)	P-value	Mean Difference (95%)	P-value
All Subjects									
Baseline		-6.46 (-15.0, 2.1)	0.140	---	---	-0.31 (-1.1, 0.5)	0.443	---	---
24		-29.8 (-48.7, -11.0)	0.002	-24.9 (-42.2, -7.5)	0.005	-1.06 (-2.11, -0.01)	0.047	-0.87 (-1.63, -0.12)	0.024
48		-32.8 (-56.9, -9.7)	0.005	-27.8 (-49.8, -5.9)	0.013	-1.28 (-2.40, -0.16)	0.025	-0.96 (-1.84, -0.08)	0.032
72		-46.8 (-76.9, -16.8)	0.002	-40.0 (-68.8, -11.2)	0.007	-1.46 (-2.73, -0.19)	0.024	-1.39 (-2.44, -0.34)	0.009
96		-35.6 (-69.7, -1.43)	0.041	-30.2 (-62.9, 2.6)	0.071	-1.35 (-2.76, 0.06)	0.061	-1.39 (-2.59, -0.2)	0.022
120		-78.2 (-117.3, -39.1)	<0.01	-70.6 (-108.3, -32.8)	<0.01	-2.51 (-4.10, -0.92)	0.002	-1.96 (-3.39, -0.54)	0.007
144		-62.5 (-110.0, -14.9)	0.010	-60.0 (-107.3, -12.7)	0.013	-2.89 (-4.73, -1.05)	0.002	-2.30 (-4.01, -0.60)	0.008
Longitudinal		-39.2 (-58.4, -19.9)	<0.01	-33.8 (-52.2, -15.4)	<0.01	-1.13 (-1.44, -0.82)	<0.01	-1.16 (-1.43, -0.89)	<0.01
Excluding Observations after Subject Experienced Virologic Failure									
Baseline		-6.5 (-15.0, 2.1)	0.140	---	---	-0.31 (-1.1, 0.48)	0.443	---	---
24		-24.1 (-43.7, -4.5)	0.016	-21.2 (-39.0, -3.4)	0.020	-0.71 (-1.79, 0.38)	0.200	-0.56 (-1.34, 0.21)	0.153
48		-21.8 (-46.0, 2.4)	0.077	-19.1 (-42.0, 3.8)	0.102	-1.00 (-2.17, 0.17)	0.094	-0.67 (-1.58, 0.24)	0.148
72		-44.1 (-75.6, -12.6)	0.006	-38.2 (-68.1, -8.2)	0.013	-1.10 (-2.42, 0.23)	0.104	-0.69 (-1.76, 0.37)	0.203
96		-40.5 (-76.4, -4.6)	0.027	-35.2 (-69.4, -0.9)	0.044	-1.67 (-3.14, -0.20)	0.026	-1.21 (-2.42, 0.00)	0.049
120		-82.0 (-125.0, -39.1)	<0.01	-74.0 (-115.3, -32.7)	<0.01	-2.57 (-4.26, -0.87)	0.003	-1.28 (-2.79, 0.23)	0.100
144		-73.6 (-124.5, -22.7)	0.005	-72.6 (-123.0, -22.1)	0.005	-3.25 (-5.21, -1.28)	0.001	-2.30 (-4.07, -0.53)	0.011
Longitudinal		-30.6 (-47.5, -13.7)	<0.01	-25.3 (-39.3, -11.3)	<0.01	-1.03 (-1.34, -0.72)	<0.01	-0.83 (-1.08, -0.57)	<0.01